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11008295 97361622 PMID: 9218583

Adenoviral gene delivery elicits distinct pulmonary-associated T helper cell responses to the vector and to its transgene.

van Ginkel F W; McGhee J R; Liu C; Simecka J W; Yamamoto M; Frizzell R A; Sorscher E J; Kiyono H; Pascual D W

Department of Microbiology and The Cystic Fibrosis Research Center, University of Alabama at Birmingham, 35294, USA.

Journal of immunology (Baltimore, Md. - 1950) (UNITED STATES) Jul 15 1997, 159 (2) p685-93, ISSN 0022-1767 Journal Code: 2985117R

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Replication-deficient adenovirus (Ad) vectors are effective to specifically target the respiratory epithelium for either corrective gene therapy such as cystic fibrosis or for mucosal immunization. As a consequence of transducing the lower respiratory tract with an E1/E3 deleted Ad5 vector, host responses have been characterized by the duration of transgene expression and by the induction of CTL responses. However, limited emphasis has been devoted to understanding the contribution of CD4+ T cell responses to the Ad vector. Both CD4+ and CD8+ T cells migrate into the lung following sequential intratracheal Ad5 transgene instillations. Isolated CD3+ T lymphocytes from the lungs were predominantly of the Th2 type, and after cell sorting, the IL-4-producing T cells were largely CD4+, while IFN-gamma expression was associated with both CD4+ and CD8+ T cells. Ab responses to the Ad5 vector and to the expressed transgene beta-galactosidase (beta gal) revealed elevated bronchial and serum IgA and IgG Abs with low neutralization titers. Analysis of serum IgG subclass responses showed IgG1 and IgG2b with lower IgG2a Abs to Ad5 and IgG2a and IgG2b Ab responses to beta gal. Ad5-specifc CD4+ T cells produced both Th1 (IFN-gamma and IL-2)- and Th2 (IL-4, IL-5, IL-6)-type cytokines, while beta gal-specific CD4+ T cells secreted IFN-gamma and IL-6. This study provides direct evidence for the concomitant induction of Th2- with Th1-type responses in both the pulmonary systemic and mucosal immune compartments to the Ad5 vector as well as a Th1-dominant response to the transgene.

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An adenovirus-simian immunodeficiency virus env vaccine elicits humoral, cellular, and mucosal immune responses in rhesus macaques and decreases viral burden following vaginal challenge.

Buge S L; Richardson E; Alipanah S; Markham P; Cheng S; Kalyan N; Miller C J; Lubeck M; Udem S; Eldridge J; Robert-Guroff M

Basic Research Laboratory, National Cancer Institute, Bethesda, Maryland 20892, USA.

Journal of virology (UNITED STATES) Nov 1997, 71 (11) p8531-41, ISSN 0022-538X Journal Code: 0113724

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Six female rhesus macaques were immunized orally and intranasally at 0 weeks and intratracheally at 12 weeks with an adenovirus type 5 host range mutant (Ad5hr)-simian immunodeficiency virus SIVsm env recombinant and at 24 and 36 weeks with native SIVmac251 gp120 in Syntex adjuvant. Four macaques received the Ad5hr vector and adjuvant alone; two additional controls were naive. In vivo replication of the Ad5hr wild-type and recombinant vectors occurred with detection of Ad5 DNA in stool samples and/or nasal secretions in all macaques and increases in Ad5 neutralizing antibody in 9 of 10 macaques following Ad administrations. SIV-specific neutralizing antibodies appeared after the second recombinant immunization and rose to titers > 10,000 following the second subunit boost. Immunoglobulin G (IgG) and IgA antibodies able to bind gp120 developed in nasal and rectal secretions, and SIV-specific IgGs were also observed in vaginal secretions and saliva. T-cell proliferative responses to SIV gp140 and T-helper epitopes were sporadically detected in all immunized macaques. Following vaginal challenge with SIVmac251, transient or persistent infection resulted in both immunized and control monkeys. The mean viral burden in persistently infected immunized macaques was significantly decreased in the primary infection period compared to that of control macaques. These results establish in vivo use of the Ad5hr vector, which overcomes the host range restriction of human Ads for rhesus macaques, thereby providing a new model for evaluation of Ad-based vaccines. In addition, they show that a vaccine regimen using the Ad5hr-SIV env recombinant and gp120 subunit induces strong humoral, cellular, and mucosal immunity in rhesus macaques. The reduced viral burden achieved solely with an env-based vaccine supports further development of Ad-based vaccines comprising additional viral components for immune therapy and AIDS vaccine development.

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11347727 98227917 PMID: 9568962

Immunological basis for protection in a murine model of tick-borne encephalitis by a recombinant adenovirus carrying the gene encoding the NS1 non-structural protein.

Timofeev A V; Ozherelkov S V; Pronin A V; Deeva A V; Karganova G G; Elbert L B; Stephenson J R

Chumakov Institute of Poliomyelitis and Viral Encephalitides RAMS, Moscow Region, Russia.

Journal of general virology (ENGLAND) Apr 1998, 79 (Pt 4) p689-95, ISSN 0022-1317 Journal Code: 0077340

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The humoral immune response to flaviviruses is mainly directed to the major envelope protein, E, and a glycosylated non-structural protein, NS1. Cell-mediated immune responses, however, appear to be directed mainly against non-structural proteins. Experiments described here show that a defective recombinant adenovirus (Rad51) containing the gene encoding the NS1 protein of tick-borne encephalitis virus can induce a strong protective immune response against several pathogenic tick-borne flaviviruses in an experimental animal model, and can enhance the efficacy of conventional vaccine preparations. A protective immune response against a lethal virus challenge can also be induced by the passive transfer of antibodies, B cells or T cells from animals vaccinated with Rad51. Raised levels of non-neutralizing antibodies and cytokines associated with a T helper cell-type 1 immune response are also observed. These data demonstrate the importance of non-structural viral proteins in the protective immune response against flaviviruses and support the use of non-structural viral proteins as vaccine components.

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File

14222379 22339270 PMID: 12450695

Vaccination with an adenoviral vector encoding hepatitis C virus (HCV) NS3 protein protects against infection with HCV-recombinant vaccinia virus.

Arribillaga Laura; de Cerio Ascension Lopez Diaz; Sarobe Pablo; Casares Noelia; Gorraiz Marta; Vales Africa; Bruna-Romero Oscar; Borras-Cuesta Francisco; Paranhos-Baccala Glaucia; Prieto Jesus; Ruiz Juan; Lasarte Juan Jose; et al

Department of Internal Medicine, Centro de Investigaciones Medicas Aplicadas (CIMA), University of Navarra, Pamplona, Spain. larribi@alumni.unav.es

Vaccine (Netherlands) Dec 13 2002, 21 (3-4) p202-10, ISSN 0264-410X Journal Code: 8406899

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: In Process

Cellular immune response plays an important role in the clearance of hepatitis C virus (HCV). Thus, development of efficient ways to induce anti-viral cellular immune responses is an important step toward prevention and/or treatment of HCV infection. With this aim, we have constructed a replication-deficient recombinant adenovirus expressing HCV NS3 protein (RAdNS3). The efficacy of RAdNS3 was tested in vivo by measuring the protection against infection with a recombinant vaccinia virus expressing HCV-polyprotein (vHCV1-3011). Immunisation with 10(9)pfu of RAdNS3 induced anti-NS3 humoral, T helper and T cytotoxic responses. We identified eight epitopes recognised by IFN-gamma producing cells, five of them exhibiting lytic activity. Moreover, we show that RAdNS3 immunised mice were protected against challenge with vHCV1-3011 and that this protection was mediated by CD8(+) cells. In conclusion, our results suggest that adenoviral vectors encoding NS3 might be useful for the induction of prophylactic and/or therapeutic anti-HCV immunity.

Record Date Created: 20021126

File

10338353 96140688 PMID: 8566039

Long-term humoral and cellular immunity induced by a single immunization with replication-defective adenovirus recombinant vector.

Juillard V; Villefroy P; Godfrin D; Pavirani A; Venet A; Guillet J G
Laboratoire d'Immunologie des Interactions Cellulaires et Moleculaires, INSERM Unite 152, Paris, France.

European journal of immunology (GERMANY) Dec 1995, 25 (12) p3467-73, ISSN 0014-2980 Journal Code: 1273201
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

This study examines the suitability of replication-defective adenovirus vectors for engineering recombinant vaccines. The immunological abilities and limitations of E1-deleted adenoviruses containing the lacZ gene (Ad-beta-gal) were investigated by examining the humoral and cellular immune responses to the beta-galactosidase protein. BALB/c mice (H-2d) were given in a single injection of recombinant adenovirus. The cytotoxic T lymphocyte (CTL) response of spleen cells was evaluated. Recognized target cells were H-2d-derived tumor cells transfected by the lac Z gene, or incubated with the 876-884 beta-galactosidase peptide known to be restricted by the Ld molecule of the major histocompatibility complex. A long-lasting beta-galactosidase-specific cytotoxic T cell response was obtained. By contrast, CTL from mice immunized with the Ld-restricted peptide were less specific for the endogenous epitope presented by the transfectants expressing beta-galactosidase. Ad-beta-gal-immunized mice were also protected against an intra-cerebral challenge with a recombinant vaccinia virus expressing the lac-Z gene. These results suggest that Ad-beta-gal-induced CTL have protective abilities in vivo. The induction of beta-galactosidase-specific T helper lymphocytes and humoral IgG responses were also examined. A proliferative response occurred only late after immunization and the primed T lymphocytes produced interleukin-2, but no interleukin-4. A humoral IgG response to the beta-galactosidase protein was detected 15-30 days after a single immunization and remained stable for 6 months without boosting. Lastly, we followed the evolution of the immune response over the course of successive immunizations. The magnitude and kinetics of the cellular and humoral responses were similar to those obtained after a single immunization. Consistent with these observations, an adenovirus-specific neutralizing antibody response was detected as early as the second immunization. Thus, a single immunization with a replication-defective adenovirus recombinant vector induces long-lasting humoral and cellular immune responses specific to the transgene product.

File

4/7/32
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09093523 20391204 PMID: 10933938
Role of vector in activation of T cell subsets in immune responses against the secreted transgene product factor IX.
Fields P A; Kowalczyk D W; Arruda V R; Armstrong E; McCleland M L; Hagstrom J N; Pasi K J; Ertl H C; Herzog R W; High K A
Department of Pediatrics, University of Pennsylvania Medical Center and The Children's Hospital of Philadelphia, 19104, USA.
Molecular therapy - the journal of the American Society of Gene Therapy (UNITED STATES) Mar 2000, 1 (3) p225-35, ISSN 1525-0016
Journal Code: 100890581
Contract/Grant No.: RO1 HL611921; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Defining immune responses against the secreted transgene product in a gene therapy setting is critical for treatment of genetic diseases such as hemophilia B (coagulation factor IX deficiency). We have previously shown that intramuscular administration of an adeno-associated viral (AAV) vector results in stable expression of therapeutic levels of factor IX (F.IX) and may be associated with humoral immune responses against F.IX. This study demonstrates that intramuscular injection of an AAV vector expressing F.IX fails to activate F.IX-specific cytotoxic T lymphocytes (CTLs) in hemostatically normal or in hemophilia B mice, so that there is an absence of cellular immune responses against F.IX. However, transgene-derived F.IX can cause B cell responses characterized by production of T helper cell-dependent antibodies (predominantly IgG1, but also IgG2 subclasses) resulting from activation of CD4+ T helper cells primarily of the Th2 subset. In contrast, administration of an adenoviral vector efficiently activated F.IX-specific CTLs and T helper cells of both Th1 and Th2 subsets, leading to inflammation and destruction of transduced muscle tissue and activation of B cells as well. Therefore, vector sequences fundamentally influence T cell responses against transgene-encoded F.IX. In conclusion, activation of the immune system in AAV-mediated gene transfer is restricted to pathways mediated by F.IX antigen presentation through MHC class II determinants resulting in T and B cell responses that are more comparable to responses in the setting of protein infusion rather than of viral infection/gene transfer.
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11896888 99339702 PMID: 10413357

Antigen-specific cytokine and antibody isotype profiles induced by mucosal and systemic immunization with recombinant adenoviruses.

Papp Z; Babiuk L A; Baca-Estrada M E

Veterinary Infectious Disease Organization, University of Saskatchewan, Saskatoon, Canada.

Viral immunology (UNITED STATES) 1999, 12 (2) p107-16, ISSN 0882-8245 Journal Code: 8801552

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

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We investigated antigen-specific antibody and T-cell responses in mice immunized with human adenovirus type 5 (HAd5) vectors expressing either the authentic or truncated form of glycoprotein D (gD and tgD, respectively) of bovine herpesvirus type 1 (BHV-1). We also tested whether different routes of immunization influenced the level and type of immunity. Immunization intranasally (i.n.) stimulated higher levels of gD-specific IgA in the lung and nasal washes and induced a higher frequency of gD-specific antibody secreting cells (CSs) in the lung than did immunization subcutaneously (s.c.). In addition, immunization i.n. stimulated gD-specific systemic antibody responses of a higher IgG1/IgG2a ratio and lower numbers of gD-specific interferon (IFN)-gamma SCs in the spleen than did immunization s.c. HAd5-specific responses also depended on the route of immunization and were characterized by lower IFN-gamma interleukin (IL)-4 ratios than gD-specific responses. Immunization with the tgD-expressing vector induced generally lower antibody and cytokine responses than the gD-expressing vector. Higher numbers of antigen-specific IgA SCs in the lung as measured by enzyme-linked immunospot (ELISPOT) assay correlated with higher levels of IgA in the respiratory tract as measured by enzyme-linked immunosorbent (ELISA) assay, although there was no such correlation for IgG responses of any isotype. In conclusion, the route of immunization and form of antigen had an impact on the level and type of immune responses induced by adenovirus vectors.

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